

**From:** [Suryanarayana Vulimiri](#)  
**To:** [Sury Vulimiri/DC/USEPA/US@EPA](#)  
**Subject:** Fwd: Fw: Re: : FA-ADME  
**Date:** 01/23/2013 10:20 PM  
**Attachments:** [FA-ADME 10-11-2012\\_Ghazi.docx](#)

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----- Forwarded message -----

From: <[Sonawane.Bob@epamail.epa.gov](mailto:Sonawane.Bob@epamail.epa.gov)>  
Date: Wed, Jan 23, 2013 at 9:59 PM  
Subject: Fw: Re: : FA-ADME  
To: Sury Vulimiri <[suryvulimiri@gmail.com](mailto:suryvulimiri@gmail.com)>

Hi Sury,

Please see below review comments on the ADME chapter by Ghazi. If you have any questions or need clarification of his comments ,please contact him.

Thanks,

Bob

-----Forwarded by Bob Sonawane/DC/USEPA/US on 01/23/2013 09:55PM -----

To: Bob Sonawane/DC/USEPA/US@EPA  
From: Ghazi Dannan/DC/USEPA/US  
Date: 01/23/2013 03:28PM  
Subject: Re: : FA-ADME

Hi Bob,

As per your request below, I have finished reviewing the attached file and provided comments and editorial changes where I thought might be appropriate. Compared to the previous draft that I last reviewed/commented on (7/12/12), I think this draft is clearer and more concise. However, I noticed that some of previous comments/suggestions were not taken into consideration. In the attached draft below, I added new comments/edits and I only repeated some of the ones (from last time) that I thought are needed.

*(See attached file: FA-ADME 10-11-2012\_Ghazi.docx)*

In addition, herein, I will try to address your specific request regarding the adequacy of the current ADME draft in response to the NAS recommendations for Chapter 3. To keep it as simple as possible, I will summarize each of the five specific issues that the NAS commented on under Conclusions and Recommendations towards the end of Section 3 of the NAS Review (pp. 44-45). And next to each of these issues, I will provide my response.

**Issue 1:** The natural occurrence of FA as a complicating factor of risk assessment: According to NAS, there is a need for improved understanding of how and when exogenous exposure to FA alters normal endogenous FA concentration. The NAS suggested having an uncertainty and variability analysis for measuring FA or

predicting target tissue concentrations across species.

(b) (5)

**Issue 2:** Due to the high reactivity of inhaled FA and its absorption by the upper respiratory tract, the weight of evidence (WOE) indicates that FA probably does not appear in the blood as an intact molecule except at doses high enough to overwhelm the tissue metabolic capacity. The NAS emphasized the need to resolve the divergent opinions in the draft IRIS assessment regarding the systemic delivery of FA.

(b) (5)

**Issue 3:** Though the NAS agrees with EPA that FA is a genotoxin and that it is reasonable to conclude that FA acts through a mutagenic MOA, another MOA, namely cytotoxicity and compensatory cell proliferation, also seem to play important roles in the FA-induced nasal tumors. Besides the EPA approach of the low-dose extrapolation (driven by mutagenicity), the NAS recommended providing alternative calculations based on nonlinearities associated with cytotoxicity and compensatory cell proliferation along with strengths and weaknesses for each approach.

(b) (5)

**Issue 4:** The NAS stated that EPA extensively evaluated several published models for evaluating the risks associated with exposure to FA. While EPA used the Computational Fluid Dynamics (CFD) model to derive human equivalent concentrations, EPA used the range used in animal studies without extrapolating to low exposures. The NAS recommended using the CFD model with extrapolation to low concentrations along with clear explanation of the the CFD approach. Though the NAS questioned the validity of other models that the EPA chose not to use, the NAS recommended revisiting and using the BBDR models by Conolly et al. (2003, 2004) and comparing the Conolly results with the current approach in the IRIS assessment along with a discussion of strengths and weaknesses for both models.

(b) (5)

**Issue 5:** In rewriting the sections in the IRIS assessment that are concerned with this chapter, the NAS recommended that EPA should consider the implications of the most recent publications using the superior analytical sensitivity (Lu et al., 2010) on measurements of DNA adducts in the older studies. The NAS considered this recent study (Lu et al., 2010) highly informative and the first to clearly distinguish between endogenous and exogenous adducts. According to the NAS, the study does not challenge the view that DNA adducts play a minor, if any, role in genotoxicity and carcinogenicity compared with the DNA-protein crosslinks; however, it adds to the evidence that FA is unable to reach distant sites. Also the NAS did not think that the positive study by Wang et al. (2009) was adequately covered and it was not clear to NAS why the study by Craft et al. (1987) was given so much emphasis.

(b) (5)



Ghazi

 Bob Sonawane---12/17/2012 09:32:52 PM---From: Bob Sonawane/DC/USEPA/US  
To: Ghazi Dannan/DC/USEPA/US@EPA

From: Bob Sonawane/DC/USEPA/US  
To: Ghazi Dannan/DC/USEPA/US@EPA  
Date: 12/17/2012 09:32 PM  
Subject: : FA-ADME

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Hi Ghazi,,

As discussed today, here is the latest draft of the ADME section of formaldehyde. I would appreciate it if you gave this a critical read to make sure that it is adequate in addressing NAS comments and incorporating more recent literature. Your review comments are expected on or before January 4, 2013. If you have any questions, please contact me.

Thanks,

Bob[attachment "FA-ADME 10-11-2012.docx" deleted by Ghazi  
Dannan/DC/USEPA/US]